

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | |
|--|------------------|---|
| <p>(51) International Patent Classification ⁷ : B01D 9/00, 9/02, B01J 19/10</p> | <p>A1</p> | <p>(11) International Publication Number: WO 00/44468</p> <p>(43) International Publication Date: 3 August 2000 (03.08.00)</p> |
| <p>(21) International Application Number: PCT/US00/01461</p> <p>(22) International Filing Date: 20 January 2000 (20.01.00)</p> <p>(30) Priority Data: 60/117,878 29 January 1999 (29.01.99) US</p> <p>(71) Applicant: BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US).</p> <p>(72) Inventors: LINDRUD, Mark, D.; 34 Peachtree Road, Basking Ridge, NJ 07920 (US). KIM, Soojin; 21 Linden Avenue, West Orange, NJ 07052 (US). WEI, Chenkou; 44 Windsor Drive, Princeton, NJ 08550 (US).</p> <p>(74) Agents: BABCOCK, Timothy, J. et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).</p> | | |
| <p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p> | | |
| <p>(54) Title: SONIC IMPINGING JET CRYSTALLIZATION APPARATUS AND PROCESS</p> | | |
| | | |
| <p>(57) Abstract</p> <p>A process is provided for the crystallization of pharmaceutical compounds by colliding a liquid jet stream (12) containing a pharmaceutical compound, such as Z-3-[1-(4-chlorophenyl)-1(4-methylsulfonylphenyl)methylene]-dihydrofuran-2-one or [R-(R*,R*)]-4-[2,4-Difluorophenyl-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl-4-thiazolyl]benzonitrile, and a solvent, such as dimethyl sulfoxide, with another liquid jet stream (14) containing an anti-solvent, such as water, within a crystallizer equipped with a mechanical stirrer (18) and at a velocity sufficient to achieve micromixing of the liquid streams. The micromixing of the liquids is subjected to ultrasonic energy (24) to promote the production of small crystals, 95 % of which have a diameter of less than one micron.</p> | | |

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|----|--------------------------|----|--|----|--|----|--------------------------|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | ML | Mali | TR | Turkey |
| BG | Bulgaria | HU | Hungary | MN | Mongolia | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MR | Mauritania | UA | Ukraine |
| BR | Brazil | IL | Israel | MW | Malawi | UG | Uganda |
| BY | Belarus | IS | Iceland | MX | Mexico | US | United States of America |
| CA | Canada | IT | Italy | NE | Niger | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NL | Netherlands | VN | Viet Nam |
| CG | Congo | KE | Kenya | NO | Norway | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NZ | New Zealand | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | PL | Poland | | |
| CM | Cameroon | KR | Republic of Korea | PT | Portugal | | |
| CN | China | KZ | Kazakstan | RO | Romania | | |
| CU | Cuba | LC | Saint Lucia | RU | Russian Federation | | |
| CZ | Czech Republic | LI | Liechtenstein | SD | Sudan | | |
| DE | Germany | LK | Sri Lanka | SE | Sweden | | |
| DK | Denmark | LR | Liberia | SG | Singapore | | |
| EE | Estonia | | | | | | |

SONIC IMPINGING JET CRYSTALLIZATION APPARATUS AND PROCESS

Related Applications

5 This application claims priority benefit under Title 35 § 119(e) of United States Provisional Application No. 60/117,878, filed January 29, 1999, and entitled SONIC IMPINGING JET CRYSTALLIZATION APPARATUS AND PROCESS, the entire contents of which are incorporated herein by reference.

Field of the Invention

10 The present invention is directed to a crystallization apparatus and process for producing submicron-sized particles.

Background of the Invention

15 Producing uniform, very small particles is a common processing challenge for pharmaceutical substances. In general, smaller particles provide two very desirable qualities of pharmaceuticals, namely higher bioavailability and a higher dissolution rate. In U.S. Pat. No. 5,314,506 there is described a method using two impinging jets to achieve uniform particles.
20 However, the particles formed using the process in U.S. Pat. No. 5,314,506 are only as small as 3 microns in size and the majority of the crystals formed are in the range of 3-20 microns.

 The general process by which these prior art small particles are produced involves two impinging liquid jets positioned within a well stirred
25 flask to achieve high intensity micromixing. At the point where the two jets strike one another a very high level of supersaturation exists. As a result of this high supersaturation, crystallization occurs extremely rapidly within the small mixing volume at the impingement point of the two liquids. Since new crystals are constantly nucleating at the impingement point, a very large
30 number of crystals are produced. As a result of the large number of crystals

formed, the average size remains small, although not all the crystals formed are small in size.

The novel apparatus and process of this invention utilizes impinging jets to achieve high intensity micromixing in the crystallization process. The background of high intensity micromixing is discussed in detail in U.S. Pat. No. 5,314,506, which is incorporated by reference herein.

10

Summary of the Invention

The present invention pertains to a novel apparatus and process for crystallizing submicron-sized particles, having an average size of less than 1 micron, and which provides high surface area end product crystals with greatly improved stability and purity. The pure, high surface area particles produced by the process of the present invention display superior crystal structure when compared with particles formed by standard slow crystallization plus milling methods known in the art which use the same quality and kind of feed compounds. These improvements in crystal structure result in decreases in decomposition rate and therefore longer shelf-life for the crystallized product or pharmaceutical composition. Moreover, the smaller size of the pharmaceutical crystals formed using the apparatus of the present invention provide for crystals having a higher bioavailability and higher dissolution rate.

More specifically, the novel apparatus and process of this invention relate to the addition of a sonication probe along with impinging jets to achieve high intensity micromixing of fluids so as to form a homogeneous composition prior to the start of nucleation in a continuous crystallization process.

The novel apparatus and process of the present invention provide for direct crystallization of high surface area submicron sized particles of high purity and stability.

Brief Description of the Drawings

FIG. 1 is a schematic diagram showing a crystal production system according to the present invention depicting two impinging jets 12, 14, an
5 agitator 18, and a sonication probe 22 positioned in a flask 16.

FIG. 2 is an enlarged sectional view of the region denoted by A in FIG. 1, illustrating the substantially diametrically opposite positioning of the impinging jet tips and the position of the sonicator probe tip within the same plane of the impinging jet tips.

10

Detailed Description of the Invention

The novel process of the present invention involves the positioning of a sonication probe or sonicator in a flask wherein liquid jets are positioned to
15 create impinging fluid jet streams to achieve high intensity micromixing of fluids prior to nucleation in a crystallization process. Two or more jets may be used to micromix two or more fluids, although it is preferable to use two jets to micromix the fluids. One liquid jet is generally a solvent saturated with product, and the other liquid jet generally contains an anti-solvent. Maximum
20 micromixing is effected when the two impinging jets are positioned substantially diametrically opposite one another, i.e., at or close to 180° from one another, and advantageously located a distance of 0.4" apart from each other.

As illustrated in FIG. 1, the impinging jet apparatus comprises a first jet
25 12 and a second jet 14 arranged substantially diametrically opposite one another in a flask 16, preferably a 1000 ml flask, which is agitated by a overhead stirrer 18. Flask 16 contains bulk or liquid 13, which is advantageously the same material as that coming through second jet 14 (anti-solvent). First jet 12 and second jet 14 are provided with jet orifices 12a
30 and 14a respectively, which are positioned substantially 180° from each other at a distance of 0.4" from one another. As illustrated in FIG. 1 and more

clearly in FIG. 2, the space 20 defined between first and second jet orifices 12a and 14a defines an impingement point where the fluid from first jet 12 and the fluid from second jet 14 impinge and micromix within flask 16.

The liquids which are pumped through first and second jets 12, 14
5 may be of different solvent composition. One fluid may be a solution of the pharmaceutical compound to be crystallized or a combination of solvents (generally referred to as "feed solution") and the other fluid may be a solvent or combination of solvents capable of initiating the compound's precipitation from solution (generally referred to as "anti-solvent"), chosen for its relatively
10 low solvation property with respect to that compound. Such solvents and anti-solvents may include but are not limited to water, methanol, ethanol, DMSO (dimethyl sulfoxide), IPA (isopropyl alcohol), DMF (dimethylformamide) or acetone.

Alternatively, the two fluids used in the process of the present
15 invention may both be solution of the pharmaceutical compound to be crystallized in the same suitable solvent or combination of solvents but each at a different temperature, and nucleation/precipitation can be initiated by instantaneous temperature reduction. A small amount of a suitable surfactant may be added to the fluids used in the process in order to alleviate
20 agglomeration which might occur during the micromixing crystallization process. Suitable surfactants which may be used include, but are not limited, to Tween 80, Cremophor A25, Cremophor EL, Pluronic F68, Pluronic F127, Brij 78, Klucel, Plasdone K90, Methocel E5, and PEG (mw 20,000) and the like.

25 A sonication probe or sonicator 22, preferably a 20 khz sonication probe, having a probe tip 24 on one end, is positioned in flask 16. Advantageously, probe tip 24 of a sonication probe 22 is immersed in the crystallization slurry throughout the crystallization process. For maximum effectiveness, probe tip 24 of sonicator 22 is advantageously located as close
30 as possible to the impinging point 20, as illustrated in FIG. 2. Depending on several processing parameter, such as temperature, liquid viscosity and

percent solids, among others, probe 24 may provide up to 500 watts of power within the crystallization slurry. The addition of ultrasonic energy in the immediate vicinity of the impinging jets 12, 14 produces an average particle size of less than 1 micron.

5 In accordance with the present invention, liquid is pumped through first and second jets 12, 14 at a minimum linear velocity of 12 m/s. The liquid is comprised of one or more solvents which may include a combination of the pharmaceutical compound and a solvent and an anti-solvent, or simply a combination of solvents and an anti-solvent. When the two jet streams
10 emerge and meet midway between orifice tips 12a, 14a high intensity micromixing occurs and a disk of crystallization slurry is formed. Depending upon the solvents and pharmaceutical compound(s) being used, each jet stream is advantageously independently maintained at a temperature in the range of 0° to 100 °C. To ensure good mixing in the bulk 13, an agitation rate
15 of >300 RPM is maintained throughout the crystallization procedure using a mixer or agitator 18, such as a Rushton turbine or other high shear impeller, although the invention is not limited in the type of mixer or agitator used. As illustrated in FIG. 1, agitator 18 is positioned within flask 16 with first and second jets 12, 14 and sonicator 22. Agitator 18 is advantageously
20 positioned proximate first and second jet 12, 14, but should not interfere with the micromixing at impingement point 20.

 Proper placement of probe tip 24 of sonicator 22 within impinging point 22 is essential. A comparison of two probe tip 24 placements has demonstrated that locating probe tip 24 lower than the jet orifices 12a, 14a,
25 and hence outside of impinging point 20, yields slightly larger crystals than if probe tip 24 is located at the same level with jet orifices 12a, 14, and hence within impingement point 20. For example, in Experiments 44032-006-12 and 44032-006-18, referenced hereinbelow in the Examples, probe tip 24 was positioned approximately one inch below the level of jet orifices 12a, 14a.
30 The resulting crystals from these batches had average sizes of 0.5164 and 0.5178 microns with 97.499% and 97.092% respectively, of the crystals less

than 0.500 microns. In contrast, in Experiment 44032-006-27, wherein probe tip 24 was positioned at the same level as jet orifices 12a, 14a and within impingement point 20, crystals were formed having an average diameter of 0.5129 microns, with 99.987% less than 0.5000 microns.

5 Regardless of the number of jets used, the jet orifices should be positioned so that the emitted fluid streams will impinge with a high intensity. Impingement of the fluids is essential so that immediate high turbulence impact is created. Thus it is crucial that when two jets are used, they must be positioned such that their orifices are substantially diametrically opposite each
10 other to facilitate proper fluid impingement.

 The following examples are provided for the purpose of illustrating the present invention and should not be construed as being a limitation on the scope or spirit of the instant invention. It should be understood that there
15 may be other embodiments which fall within the spirit and scope of the invention as defined by the claims appended hereto.

EXAMPLE 1

20 Crystallization of (Z-3-[1-(4-chlorophenyl)-1-(4-methylsulfonylphenyl)methylene]-dihydrofuran-2-one
 Experiment No. 42216-195

 (1) 152.5 grams of the pharmaceutical compound were dissolved in 300 ml of DMSO at 65-75 °C. 1200 ml of water (RO quality, filtered) was
25 chilled at 2 °C. The rich solution and water were both charged to agitated, jacketed vessels. The respective temperatures of the contents were maintained by heating or chilling the jackets. The process fluids were circulated through the feedlines to attain steady state temperatures and flow rates.

30 (2) 300 ml of water (RO quality, filtered) was charged to the impinging vessel. The jacket temperature was maintained at 2 °C throughout the crystallization.

(3) With the mechanical stirrer and sonication power at maximum level, the solution and water jets were impinged at a 1:4 mass flow rate. The rich solution's flowrate was 0.18 kg/min through a 0.020" nozzle and the water flowrate was 0.72 kg/min through a 0.040" nozzle.

5 (4) Upon completion of crystallization, the product was filtered and then washed with approximately 100 ml water (RO quality, filtered). The filter cake was dried in vacuo at 70 °C until dry. Yield is 89.4% excluding 24.19 grams recovered from the solution vessel and circulating lines.

10 (5) The dry product was delumped by passing it through an 80 mesh screen. API aerosizer assays yield a mean particle size of 0.54 microns with 95% of particles under 0.94 microns.

Summary of Experiments with BMS-225969

| | <u>Experiment No.</u> | <u>Mean Size</u> | <u>%<0.5000 μm</u> | <u>95th percentile</u> |
|----|-----------------------|------------------|--------------------------------------|------------------------|
| 15 | 42216-157-20 | 0.5090 microns | 99.011 | 0.5086 microns |
| | 42216-158 | 0.5124 | 98.097 | 0.5087 |
| | 42216-195 | 0.5376 | 92.224 | 0.9373 |
| | 44032-006-12 | 0.5164 | 97.499 | 0.5087 |
| | 44032-006-18 | 0.5178 | 97.092 | 0.5088 |
| 20 | 44032-006-27 | 0.5129 | 97.987 | 0.5087 |

EXAMPLE 2

25 Crystallization of [R-(R*, R*)]-4-[2-[2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl-4-thiazolyl]benzonitrile
Experiment No. 42216-027

30 (1) 50 grams of the pharmaceutical compound were dissolved in 150 ml of DMSO at 70 °C and the solution was polish filtered. 1000 ml of water (RO quality, filtered) was tempered to 20 °C. The rich solution and water were both charged to agitated, jacketed vessels. The respective temperatures of the contents were maintained by heating or chilling the jackets. The process fluids were circulated through the feed lines to attain steady state temperatures and flow rates.

(2) 300 ml of water (RO quality, filtered) was charged through the impinging vessel. The jacket temperature was maintained at 20 °C throughout the crystallization.

(3) With the mechanical stirrer and sonication power at maximum level, the solution and water jets were impinged at a 1:4 mass flow rate. The solution's flow rate is 0.18 kg/min through a 0.020" nozzle and the water flowrate is 0.72 kg/min through a 0.040" nozzle.

(4) Upon completion of crystallization, the product was filtered and washed with 2 liters of water (RO quality, filtered). The filter cake was dried in vacuo at 70 °C until dry.

(5) The dry product was delumped by passing it through an 80 mesh screen. API aerosizer assays yield a mean particle size of 0.5324 microns with 95% of particles under 0.8321 microns.

| <u>Experiment No.</u> | <u>Mean Size</u> | <u>%<0.5000 μm</u> | <u>95th percentile</u> |
|-----------------------|------------------|--------------------------------------|------------------------|
| 42216-028-10 | 0.5324 microns | 91.563 | 0.8321 microns |

Claims

What is claimed is:

5 1. A process for the crystallization of a pharmaceutical compound comprising positioning a tip of a sonication probe within a gap defined between two or more fluid jets positioned such that fluid jet streams which emerge from said fluid jets impinge in said gap creating a point of high turbulence at the point of impact of said fluid streams, each of said fluid
10 streams having sufficient linear velocity to achieve high intensity micromixing of the solutions prior to nucleation, said sonication probe providing ultrasonic energy in the immediate vicinity of said impinging fluid streams so as to effect nucleation and the direct production of small crystals, at least 95% of said crystals having a diameter of less than 1 micron.

15

 2. The process according to claim 1, wherein two fluid jets are used, said first fluid jet is provided for carrying a first fluid stream, said first fluid stream comprising a combination of DMSO and said pharmaceutical compound, said second fluid jet is provided for carrying a second fluid
20 stream, said second fluid stream comprising water .

 3. The process according to claim 2, wherein said first and said second fluid jets are substantially diametrically opposed to each other, such that said first and second fluid streams impinge so as to attain high intensity
25 impact.

 4. The process according to claim 1, wherein at least one of said fluid streams comprises a surfactant.

30

5. The process according to claim 1, wherein said pharmaceutical compound selected from (Z-3-[1-(4-chlorophenyl)-1-(4-methylsulfonylphenyl)methylene]-dihydrofuran-2-one, and [R-(R*, R*)]-4-[2-
5 [2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl-4-thiazolyl]benzonitrile.

6. The process according to claim 1, wherein each jet stream is independently at a temperature in the range of about 0 °C to 100 °C.

10

7. The process according to claim 1, wherein substantially all of said crystals have a diameter equal to or less than 1 micron.

8. The process according to claim 1, wherein said gap defined
15 between said fluid jets is 0.4 inches.

9. The process according to claim 1, wherein said tip of said sonication probe is positioned in said gap in the same plane with said fluid jets and at the point where said fluid streams from set fluid jets impinge with
20 one another.

10. The process according to claim 9, wherein said sonication probe provides power in a range of between 30 and 150 watts.

25 11. A crystallization apparatus for producing submicron-sized particles, which comprises:

a crystallization flask;

two or more fluid impinging jets,

an agitator, and

30 a sonication probe having a probe tip, wherein said impinging jets, said agitator and said sonication probe are positioned within said

crystallization flask, said impinging jets positioned substantially diametrically opposed to each other, and said sonication probe positioned proximate said impinging jets such that said probe tip is positioned such that it is at the same level as the impinging jets.

5

12. The crystallization apparatus according to claim 11, wherein said apparatus comprises two fluid impinging jets, said first fluid jet is provided for carrying a first fluid stream, said first fluid stream comprising a combination of DMSO and a pharmaceutical compound, said second fluid jet
10 is provided for carrying a second fluid stream, said second fluid stream comprising water .

13. The crystallization apparatus according to claim 12, wherein said first and said second fluid jets are substantially diametrically opposed to
15 each other, such that said first and second fluid streams impinge so as to attain high intensity impact.

14. The crystallization apparatus according to claim 11, wherein said agitator provides an agitation rate of >300 rpm which is maintained
20 throughout the crystallization process.

15. The crystallization apparatus according to claim 11, wherein sonication probe is a 20 khz probe.

25 16. The crystallization apparatus according to claim 15, wherein said sonication probe provides power to said first and said second fluid streams within said flask in the range from 30 to 50 watts.

17. The process according to claim 11, wherein said pharmaceutical
30 compound selected from (Z-3-[1-(4-chlorophenyl)-1-(4-methylsulfonylphenyl)methylene]-dihydrofuran-2-one, and [R-(R*, R*)]-4-[2-

[2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl-4-thiazolyl]benzonitrile.

1 / 2

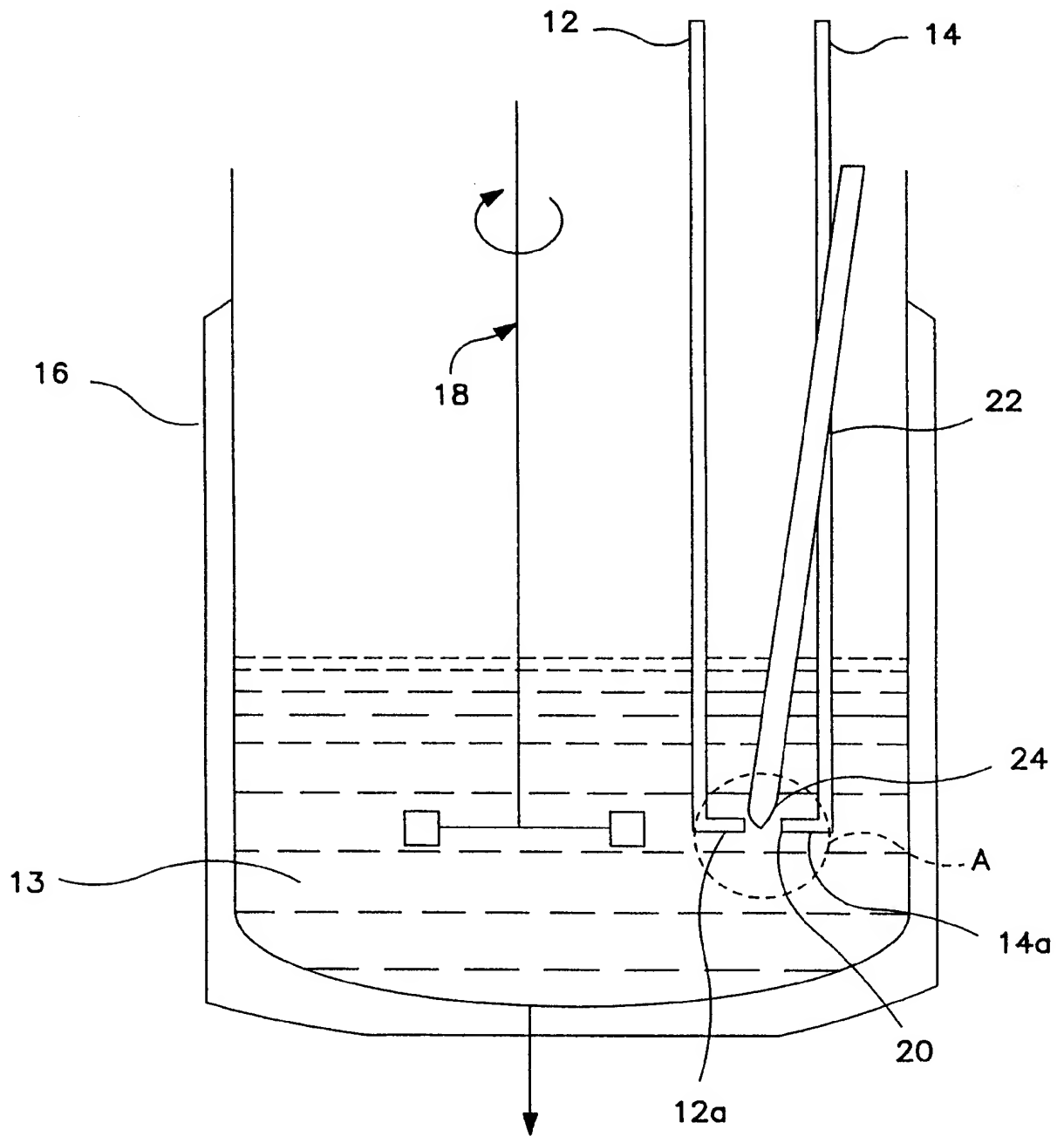


FIG. 1

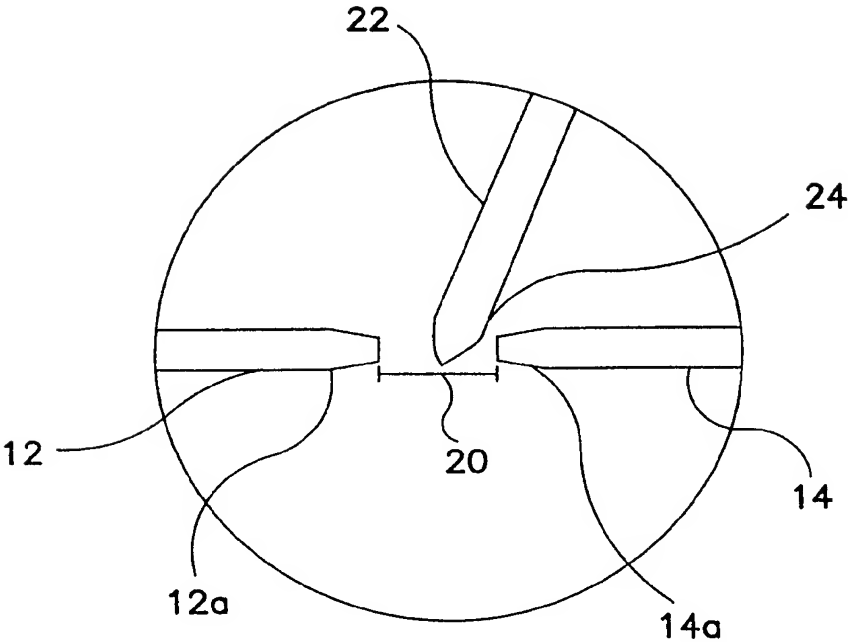


FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/01461

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :B01D 9/00, 9/02; B01J 19/10

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 23/295R, 299; 204/157.62; 239/421, 433; 366/173.1; 422/245.1; 423/659

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CONTENTS OF U. S. PATENT APPLICATION No. 07-793,764 (NOW U. S. PATENT No. 5,314,506

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| Y | US 5,314,506 A (MIDLER, JR. et al) 24 May 1994, col. 1 lines 37-40, col. 2 lines 49-50, col. 5 lines 1-57, Example 1, claims 1 and 4 and Figure 5. | 1-17 |
| Y | EP 0 275 607 A1 (BELLAMY) 27 July 1988, page 2, col. 1 lines 20-32. | 1-17 |
| A | CH 671,166 A5 (GARBAGNATI) 15 August 1989, English abstract. | 1-17 |
| A | US 2,876,083 A (PRIETL) 03 March 1959, claims 1-17. | 1-17 |



Further documents are listed in the continuation of Box C.



See patent family annex.

| | |
|---|--|
| * Special categories of cited documents: | "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "A" document defining the general state of the art which is not considered to be of particular relevance | "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "B" earlier document published on or after the international filing date | "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "Z" document member of the same patent family |
| "O" document referring to an oral disclosure, use, exhibition or other means | |
| "P" document published prior to the international filing date but later than the priority date claimed | |

Date of the actual completion of the international search

07 MARCH 2000

Date of mailing of the international search report

06 APR 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

TIMOTHY C. VANOY

Telephone No. (703) 308-2540

INTERNATIONAL SEARCH REPORT**International application No.**
PCT/US00/01461**C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------------|---|------------------------------|
| A | LIU, P. et al. "The Use of Continuously Impinging Jets to Control Crystallization and Particle Size in Pharmaceutical Manufacturing" presented at the American Institute of Chemical Engineers' National Meeting on November 1990 in Chicago, Illinois, English abstract (only). | 1-17 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/01461

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

23/295R, 299; 204/157.62; 239/421, 433; 366/173.1; 422/245.1; 423/659